Main Regularities of Mutual Location of Different Pacemaker Cells in the Rat Heart Sinoatrial Node

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The distribution of pacemaker cells and atrial working cardiomyocytes in the anterior right atrial wall was studied using intracellular glass microelectrodes under conditions of short-term culturing. It was shown that the dominant pacemaker region and the functional tail are located in the lateral area of the central part of the sinoatrial node, while the medial area is occupied by latent pacemaker cells.

Key Words: *sinoatrial node; pacemaker cells; sinus node artery; intracellular lead; action potentials*

The sinoatrial nodes (SAN) are located around and along the SAN artery in the majority of mammals, including humans. This structure of SAN implies certain peculiarities of their architecture, functioning, and regulation of their work. For example, pulse beats, rhythmically deforming the wall of the SAN artery, modulate the work of pacemaker cells (PMC) [6]. A unidimensional analysis of PMC distribution along the SAN artery showed high polymorphism of action potential curves of these cells. The central part of SAN was detected, which consists of true and latent PMC with similar forms of action potentials, and the peripheral part, consisting of latent PMC, whose action potentials represent a great variety of transitional forms between the true PMC and the neighboring atrial working cardiomyocytes [1]. In addition, autoradiographic analysis of ^{3}H-dihydral prenolol, ^{3}H-QNB, ^{3}H-DAGO, and ^{3}H-dopamine binding has shown obvious heterogeneity in the distribution of β-adrenoreceptors, muscarinic cholinoreceptors, and dopamine receptors in the central part of SAN [2-4].

We analyzed spatial distribution of PMC with different forms of action potentials on the surface of the anterior right-atrial wall in the SAN region in order to detect the probable correlations between the density of receptor structures and presence of PMC with this or that form of action potentials.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats (n=19; 80-140 g). Before the analysis, the animals were sacrificed by intraperitoneal phenobarbital (60 mg/kg). The thorax was opened and 10 ml 0.01% trypan blue in Hanks' solution (pH 7.35, t=37-38°C) was slowly injected into the left ventricle. The heart was removed and plunged in a cuvette with Hanks' solution (15-20°C); a fragment of the right atrium containing the anterior wall, right cranial and caudal venae cavae, and the auricle was mobilized. The SAN was located at the interface between the vena cava superior and the auricle in the direction of the SAN artery, which was visualized by trypan blue. The preparation was then fixed and placed into a flow cuvette with modified Krebs—Ringer solution saturated with 5% carbogen to pH of 7.4 and incubated at 38°C. The medium in the cuvette was replaced at a rate of 1.7 ml/min. The shape of true and latent PMC action potentials was evaluated using glass microelectrodes. Two-dimensional coordinates of the true and latent PMC and of the working atrial cardiomyocytes were recorded by means of

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successive introduction of microelectrodes, monitored under an MBI-3 light microscope, on the scheme of the right atrium preparation, sketched beforehand on millimeter paper. The results of the experiments were statistically processed using Student's *t* test.

RESULTS

The distribution of true and latent PMC and atrial cardiomyocytes in the right atrial anterior surface in the periarterial region (Fig. 1) confirmed previous results [1]. Since there was no apparent branching (Fig. 1, *a*) or just a caudal branching of the SAN artery (Fig. 1, *b*), it was impossible to precisely locate the dominant pacemaker region (DPR), which in the studied preparations could be detected only electrophysiologically. By contrast, cranial branching of the SAN artery, both uneven (Fig. 1, *c*) and even (Fig. 1, *d*), was the marker of DPR location at the site of dichotomy.

Analysis of PMC distribution in the anterior surface of the right atrium showed that the majority of true PMC were located in the immediate vicinity of the SAN artery wall. It is of paramount importance that these cells are always located on the side of the artery bordering the right cranial vena cava (Figs. 1, 2), in the SAN lateral area, described previously in studies of the distribution of receptor structures in the central part of SAN [2-4]. Latent PMC with action potential form similar to that of true PMC, but differing from it by a more abrupt transition from the slow diastolic depolarization (phase 4) to initial rapid elevation of potential (phase 0) and higher rate of the

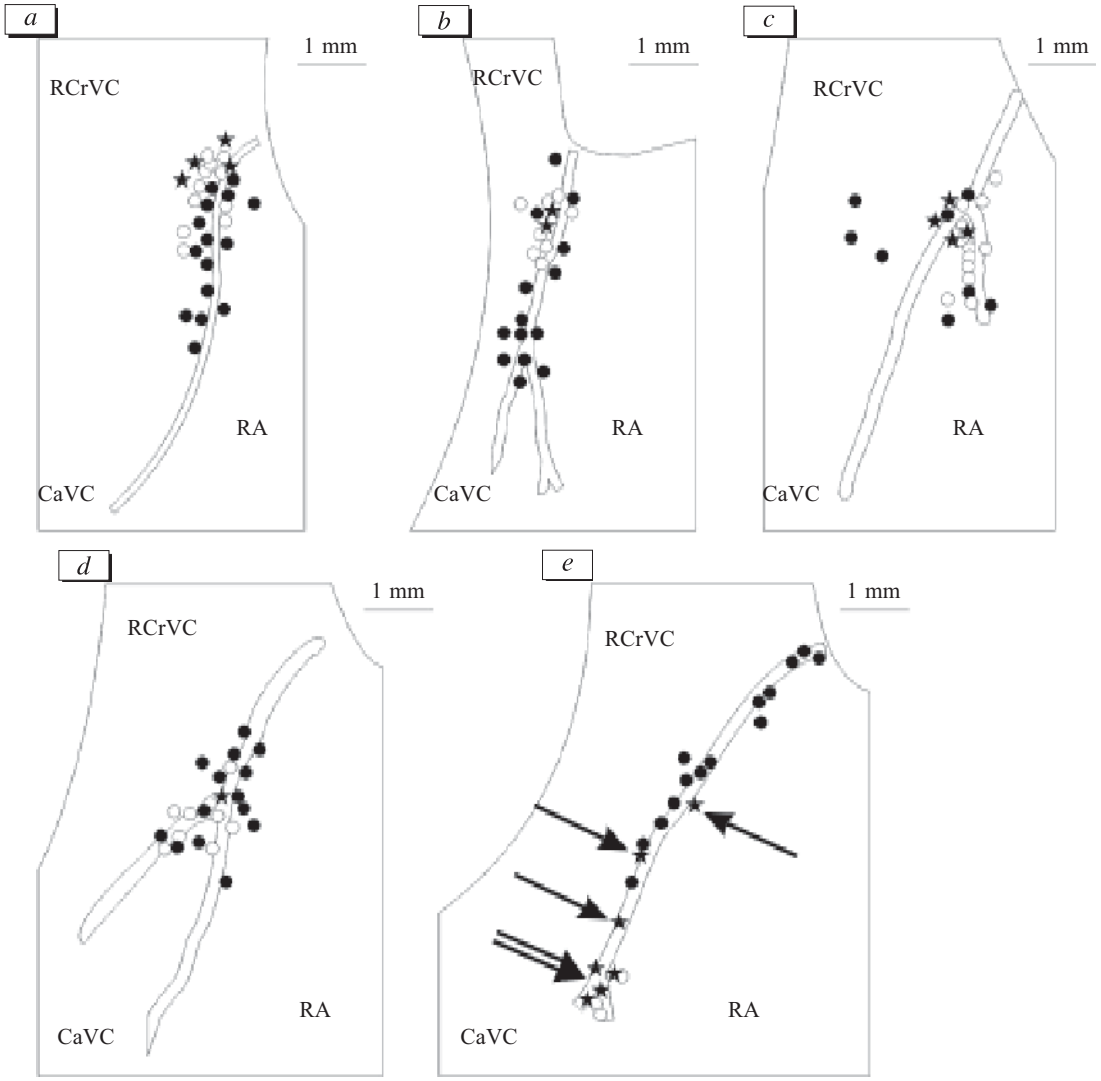

Fig. 1. Mutual location of true PMC (asterisks), latent PMC (light circles), and working atrial cardiomyocytes (dark circles) near the SAN artery on the scheme of the right atrial anterior surface. *a*) no branching of SAN artery; *b*) caudal branching of SAN artery; *c*) cranial branching of SAN artery (variant of origination of a smaller branch from the artery); *d*) cranial branching of SAN artery (dichotomy of the artery); *e*) DPR at the site of caudal branching of SAN artery. RCrVC: right cranial vena cava; CaVC: caudal vena cava; RA: right auricle. Single arrow: accessory true PMC; double arrow: DPR.

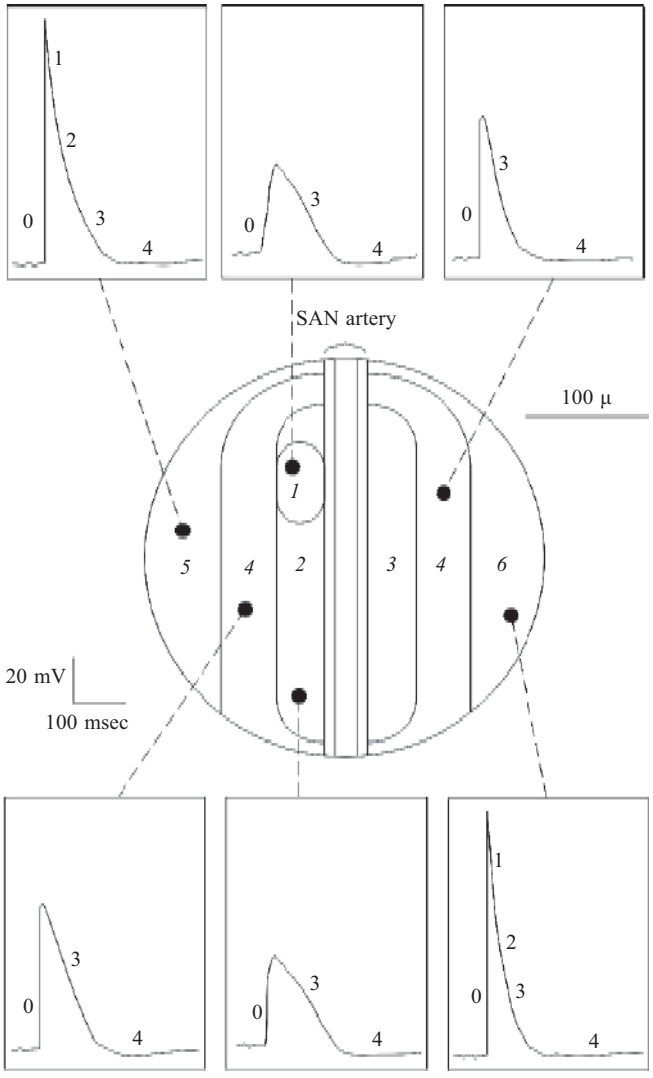

Fig. 2. Mutual location of true PMC (*1*), latent PMC (*2*, *4*), and working atrial cardiomyocytes (*5*, *6*) on the scheme of the rat heart SAN central part. The lateral area of SAN central region: *1*) functional nucleus of SAN central part (DPR); *2*) functional tail of SAN central part; *3*) medial area of SAN central part (SAN periphery); *5*) RCrVC; *6*) RA. Action potential curves: 0: initial rapid elevation phase; 1, 2, 3: repolarization phases; 4: diastole phase (slow diastolic depolarization phase for true and latent PMC).

potential increase during phase 0, were also located in the lateral area, forming a functional tail of the central part of SAN (Figs. 1, 2). However, importantly that in some cases some true and latent PMC forming the lateral region of the SAN central part were not directly neighboring the wall of the SAN artery, being located at some distance from it (Fig. 1, *a*, *b*). This indicates that generally the lateral area should be regarded as a bulky formation with the final dimensions adjacent to the wall of the SAN artery (Fig. 2). The functional nucleus of SAN was extremely rarely located in the region of caudal dichotomy of the SAN artery (Fig. 1, *e*). The location of DPR, detected in our experiments, was associated with the appearance of foci of accessory dominant PMC higher along the artery. This multifocal location of the true PMC can presumably be responsible for the appearance of arrhythmia.

The medial area of the central part of SAN (Fig. 2), in turn, has several latent PMC (Fig. 1) with action potential form more characteristic of SAN periphery (Fig. 2). It is noteworthy that this area is also characterized by accumulation of dopamine receptors with maximum density in the zone contralateral to DPR [4]. These dopamine receptors belong to the D_2-like subtype and are located on the cytolemmas of autonomic postganglionic neurocyte processes [5]. The presence of potent accumulation of autonomic postganglionar conductors in the SAN medial area *vis-a-vis* the functional nucleus indicates that this region is actively involved in the regulatory activity of SAN [4]. In addition, it is also probable that nerve receptor formations, recording the main parameters of cardiovascular function, are also located in this area. We previously suggested that the zone of the maximum density of dopamine reception *vis-a-vis* the functional nucleus in the ontogenesis determines the location of DPR and induced the branching of SAN artery [4]. The actual functional significance of the medial area of the SAN central part can become the object of further research.

REFERENCES

1. P. V. Sutyagin, E. E. Kalinina, and A. S. Pylaev, *Byull. Eksp. Biol. Med.*, **139**, No. 2, 227-230 (2005).
2. P. V. Sutyagin, E. E. Kalinina, and A. S. Pylaev, *Ibid.*, **140**, No. 7, 104-108.
3. P. V. Sutyagin, E. E. Kalinina, and A. S. Pylaev, *Ibid.*, **140**, No. 8, 210-214.
4. P. V. Sutyagin, E. E. Kalinina, and A. S. Pylaev, *Ibid.*, **140**, No. 10, 472-477.
5. F. Amenta, A. Ricci, S. K. Tayebati, and D. Zaccheo, *Ital. J. Anat. Embryol.*, **107**, No. 3, 145-167 (2002).
6. T. N. James, *Prog. Cardiovasc. Dis.*, **45**, No. 4, 327-360 (2003).